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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BURKHART, MICHAEL D	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
05/14/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No.	Applicant(s)	
	10/655,872	BEAR ET AL.	
	Examiner	Art Unit	
	Michael Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38, 58-60, 124-130, 132, 136-145, 152 and 153* is/are pending in the application.

4a) Of the above claim(s) *25,26 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24, 27-30, 32-38, 58-60, 124-130,132, 136-145, 152 and 153* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/12/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on 2/7/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election without traverse of the species of RNA polymerase III promoters in the reply filed on 2/11/2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 25-26 and 31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/11/2009.

Claim 24 has been rejoined in light of the teachings of Miyoshi et al (see below).

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or

provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos. 60/414,195 and 60/408,558, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Independent claims 1, 124, 152 and 153 recite lentiviral vectors comprising, *inter alia*, an HIV FLAP element, two MCS sites, and in claims 1 and 124, a target site for a site specific recombinase and a expression-enhancing posttranscriptional regulatory element. A review of the '195 and '558 applications reveals no mention of an HIV FLAP element, two MCS sites, the use of any general site-specific recombinase site, nor the use of any general element that might be considered expression enhancing in a posttranscriptional manner (the applications do disclose the use of the Cre/lox recombinase system and the WRE element). Regarding dependent claims, the '195 and '558 applications do not disclose vectors comprising any given heterologous promoter, or a genus of RNA polymerase III promoters, but rather only teach the use of the CMV and murine U6 (RNA pol III) promoters. There are no teachings of including the list of restriction sites found in claims 9 and 10 in the vectors, nor of vectors having the range of sizes listed in claims 17-21 and 136-143. There are no teachings of using a genus of reporter molecules as recited in claim 35, only the use of EGFP, and no specific teachings of the cell types recited in claim 145, other than the E10 and 293T cells. Thus, the invention is given a priority date of 11/21/2002, the filing date of the 60/428,039 application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 124 and 132 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 124, the phrases "for example (e.g.)" and "such as" render the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 132 recites the limitation "the promoter" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 7-9, 12, 16-24, 32-35, 38, 58-60, 124, 125, 132, 136 and 145 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyoshi et al (J. Virol., 1998) as evidenced by Naldini et al (Science, 1996) and Naldini B (PNAS, 1996).

Miyoshi et al teach retroviral vectors comprising a SIN LTR, a packaging signal, and a MCS. See Fig. 1, the abstract, and page 8151, first column, first and second full ¶'s. The vectors of Miyoshi et al were constructed using the pHR' vector of Naldini et al, which inherently has the Psi packaging signal and RRE (Fig. 1 of Naldini et al the "transfer vector"). The RRE is considered an expression-enhancing posttranscriptional regulatory element because it facilitates transport of vector transcripts out of the nucleus (page 263, third column of Naldini et al), and due to the lack of any limiting definition of such an element in the specification. The instant specification provides no limiting definition of what is to be considered a MCS, other than it must contain restriction sites that are unique or found infrequently in the remainder of the vector. Further, it does not provide a means for distinguishing what is to be considered a "first" MCS and a "second" MCS. Thus, it appears arbitrary what can be considered first and second MCS sites as long as they contain certain restriction sites that can be used to clone a desired nucleic acid sequence. The MCS constructed by Miyoshi et al comprises 10 restriction sites: the first 5 are considered a first MCS, and the last five (5'-3') are considered the second. Alternatively, Miyoshi et al used various sites in the LTR (*MluI, BspEI, ApaI*) to prepare the SIN LTR, these sites are also considered a second MCS with respect to the first MCS above. Miyoshi et al inserted heterologous DNA (e.g. GFP, the SIN LTR) sequences into these sites. Four unique sites introduced into the MCS of Miyoshi et al were *XhoI, XbaI, HpaI and BamHI*. See the plasmid construction ¶'s mentioned above. Naldini et al consider the pHR' a "transfer" plasmid, thus the

vectors of Miyoshi et al (used for the same purpose: to package a desired lentiviral genome bearing a transgene) are also considered a "transfer" plasmid. Neither Miyoshi or Naldini et al list the exact size of the plasmids, but Miyoshi et al teach that the majority of the plasmid, even with the GFP transgene inserted, is around 4kb (Fig. 1, LL-CG transcript, right-hand side), and this does not take into account other necessary plasmid elements such as an origin of replication and a prokaryotic selection marker. It is thus considered the vectors/plasmids of Miyoshi et al were less than 6kb, and "approximately" 5,830 bp.

Miyoshi et al produced infectious viral particles comprising the transfer vectors (page 8151, first column, second full ¶, and the second column, third full ¶). Certain vectors of Miyoshi et al comprised the heterologous CMV promoter (e.g. Fig. 1), considered to be inserted into the second MCS (page 8151, first column, first full ¶). Regarding claim 32, the HIV LTR is considered a heterologous promoter with respect to the human 293T cells used to produce the viruses, and thus is the second heterologous promoter in the vectors. Regarding claim 33, GFP (linked to the CMV promoter) is considered a selectable marker and a reporter molecule, as it can be used to select cells (e.g. with FACS), and was used by Miyoshi et al to detect expression from the virions (e.g. Fig. 4). Regarding claim 38, the vector elements already described, and the selective properties of GFP, are considered to be genetic elements that can stably maintain the vector as an episome in mammalian cells, lacking a definition of such elements in the specification. See Figs 4 and 5, and page 8155, first column, first ¶ of Miyoshi et al. Regarding the cell claims 58-60, 293T cells were used to produce and titer the virions, along with plasmids encoding Gag, Pol and Env proteins (page 8151, first column, second full ¶). Regarding the kit claim (124), kits are considered to be a localized collection of reagents, thus, a teaching of the kit

components is considered a teaching of a kit. Miyoshi et al teach the vector and cell components of claim 124 for reasons set forth above. For virion production methods, Miyoshi et al reference Naldini B, thus it is considered that Miyoshi et al inherently used the components and methods of Naldini B when preparing virions. Naldini B teach using the transfection-enhancing reagent calcium phosphate (page 11382, second column, last ¶). The p24 antigen ELISA assay used by both Miyoshi and Naldini B et al is considered to be a "selection agent" as it was used to select high titer stocks of virions. The Miyoshi et al reference is considered to be "instructions for use" as it contains all the information needed to use the kit components. The pCMVΔR8.2 plasmid (Miyoshi et al, page 8151, first column, second full ¶ and Naldini B et al, Fig. 1) is considered a positive control plasmid as it express p24 antigen and could be used as a positive control in p24 ELISA assays.

Claim are 1-8, 11-18, 22, 23, 32-35, 38, 58-60, 124-127, 130, 132, 136-14145, 152 and 153 are rejected under 35 U.S.C. 102(e) as being anticipated by Trono et al (US 7,198,950, EFD 10/2/2001).

Trono et al teach retroviral vectors comprising a SIN LTR, a Psi packaging signal, two MCS sites, loxP recombinase sites, a WRE expression enhancing element, and an HIV FLAP element. See Figs. 1A, 5, 6, 6B, the abstract, column 3, lines 9-11, column 5, lines 48-60, column 12, lines 1-29, column 13, lines 31-46, column 35, lines 10-15. The vectors of Trono et al comprised a cPPT (e.g. Fig. 1 of Trono et al and column 4, lines 43-50, SEQ ID NO: 1). The cPPT is considered to be an HIV FLAP element as it comprises the components of such an element as set forth in the instant specification: i.e. the cPPT and a central termination sequence

or CTS. The CTS is considered to be the AAAAATT and AAATTTT termination sequences at the 3' end of SEQ ID NO: 1 of Trono et al. Trono et al inserted heterologous DNA (e.g. the gp91 promoter, HS-12, HS-14) sequences into these sites (Figs. 6B and C). Trono et al consider their plasmids "transfer" plasmids (column 18, lines 21-23). Trono et al list teach one of their plasmids to be less than 9 kb (e.g. Fig. 5). It is thus considered the vectors/plasmids of Miyoshi et al were less than 6kb, and "approximately" 5,830 bp.

Trono et al produced infectious viral particles comprising the transfer vectors (columns 17 and 35). Certain vectors of Trono et al comprised the heterologous gp91 promoter (e.g. Figs. 5-6), considered to be inserted into the second MCS (Fig. 6A or 6B), and may comprise the CMV promoter (column 12, lines 46-55). Regarding claim 32, the HIV LTR is considered a heterologous promoter with respect to the human 293 cells used to produce the viruses, and thus is the second heterologous promoter in the vectors. Regarding claim 33, GFP (linked to the gp91 promoter, Fig. 6A) is considered a selectable marker and a reporter molecule, as it can be used to select cells (e.g. with FACS, Figs. 2 and 3), and was used by Trono et al to detect expression from the virions. Enhanced GFP, or EGFP is taught in column 12, lines 29-31. Additional selection and detectable markers are taught in the ¶ linking columns 29 and 30. Regarding claim 38, the vector elements already described, and the selective properties of GFP, are considered to be genetic elements that can stably maintain the vector as an episome in mammalian cells, lacking a definition of such elements in the specification. Regarding the cell claims 58-60, 293T cells (at least) were used to produce and titer the virions, along with plasmids/cells encoding Gag, Pol and Env proteins (column 17, lines 21-57, column 34, lines 36-44, column 35). Regarding the kit claim (124), kits are considered to be a localized collection of reagents, thus, a

teaching of the kit components is considered a teaching of a kit. Trono et al teach the vector and cell components of claim 124 for reasons set forth above. For virion production methods, Trono et al teach using the transfection-enhancing reagent calcium phosphate and selection markers and agents (column 17, lines 4-20, column 35) to prepare and titer viral stocks. The Trono et al patent is considered to be "instructions for use" as it contains all the information needed to use the kit components. The plasmids used in Fig. 2A to express GFP are considered positive control plasmids as they express the marker (GFP) used in the titration assays. Regarding claims 136-143, Trono et al teach the lentiviral genomes (i.e. as found in the virus particles, essentially the sequence found between the LTRs) to be anywhere from approximately 5,830 to 7,975 base pairs depending on the number and type of promoter and transgene inserted into the vector (Fig. 6, column 4, lines 13-29, column 6, line 35 to column 7, line 49, Example 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Note, "NpeI" in claim 128 is interpreted to be "NheI" as no restriction site or enzyme termed "NpeI" is taught by the instant specification, nor the prior art. Further, NheI is recited in claims 9 and 10.

Claims 10, 128, and 129 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Miyoshi et al (J. Virol., 1998) or Trono et al (7,198,950) in view of Lowery (U.S. 6,828, 102, EFD 11/20/2001) and Parrot et al (U.S. 6,096,523, 8/1/2000).

The teachings of Miyoshi and Trono et al are as above and applied as before. In addition, Trono et al teach that the design of MCSs is one of design choice and depends upon the needs of the skilled artisan for a particular vector and transgene, for example. Use of the restriction sites found within an MCS are widely understood by those of skill in the art See column 28, line 53 to column 29, line 5. Neither Miyoshi not Trono et al teach the use of the specific enzymes found in claims 128 and 129.

Lowry teaches that the restriction enzymes and their associated sites recited in claim 129 were known in the art prior to the instant filing date. See Table 3 and Fig. 1, for example.

Parrot et al teach that the restriction enzymes and their associated sites recited in claim 128 were known in the art prior to the instant filing date. See Tables 1 - 3, for example.

The claimed vectors are essentially disclosed by Miyoshi and Trono et al with the exception of the specific restriction site limitations. The ordinary skilled artisan, seeking a vector comprising the sites recited in claims 128 and 129, would have been motivated to use these specific sites with the vectors of Miyoshi and Trono et al because Trono et al teaches the utility of using literally any known restriction site to generate a MCS based upon the needs of the skilled artisan. It would have been obvious for the skilled artisan to do this because of the known benefit of generating such vectors for expression of transgenes as taught by Miyoshi and Trono et al. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 27-29, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Miyoshi et al (J. Virol., 1998) or Trono et al (7,198,950) in view of Devroe et al (BMC Biotech, 8/2002, cited by applicants).

The teachings of Miyoshi and Trono et al are as above and applied as before. In addition, Trono et al teach that the design of SIN vectors is flexible and can be accommodated to express literally any heterologous DNA or RNA sequence desired. Neither Miyoshi not Trono et al teach the use of RNA polymerase III promoters.

Devroe et al teach a retroviral vector to express siRNA comprising a U6 RNA polymerase III promoter. See Figure 1 and the abstract.

The claimed vectors are essentially disclosed by Miyoshi and Trono et al with the exception of the RNA polymerase III promoter limitation. The ordinary skilled artisan, seeking a vector to express siRNA, would have been motivated to use the vectors of Miyoshi et al and Trono et al because Devroe and Trono et al teach the utility of using such vectors to express a given RNA or siRNA sequence. It would have been obvious for the skilled artisan to do this because of the known benefit of using a U6 promoter to express siRNA as taught by Devroe et al. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Miyoshi, Trono and Devroe et al as applied to claims 27-29, 36 and 37 above, and further in view of Caplan et al (US 20030149113 A1, EFD 10/12/2001).

The teachings of Miyoshi, Trono, and Devroe et al are as above and applied as before. None of these references teach using the HI RNA polymerase III promoter.

Caplan et al teach the use of the U6 or H1 RNA polymerase III promoter to express siRNA molecules. See ¶ [0183].

The claimed vectors are essentially disclosed by Miyoshi, Trono and Devroe et al with the exception of the H1 RNA polymerase III promoter limitation. The ordinary skilled artisan,

seeking a vector to express siRNA, would have been motivated to use the H1 promoter of Caplan et al with the vectors of Miyoshi, Trono and Devroe et al because Caplan et al teach the interchangeability of using such RNA polymerase III promoters to express a given siRNA sequence. It would have been obvious for the skilled artisan to do this because of the known benefit of using a RNA polymerase III promoter to express siRNA as taught by Devroe and Caplan et al. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhart whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhart/
Primary Examiner, Art Unit 1633